Reproductive History, Oral Contraceptive Use, and the Risk of Ischemic and Hemorrhagic Stoke in a Cohort Study of Middle-Aged Swedish Women

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Background and Purpose—Controversy persists as to whether oral contraceptive (OC) use and reproductive history play a role in the etiology of stroke, particularly ischemic stroke. Our aim was to investigate this question in a cohort of middle-aged Swedish women.

Methods—The Women’s Lifestyle and Health Cohort Study included 49,259 Swedish women, aged 30 to 49 years at baseline (1991 to 1992). Participants completed an extensive questionnaire and were traced through linkages to national registries until the end of 2004.

Results—Among the 45,699 women included in these analyses, there were 285 cases of incident stroke during follow-up (193 ischemic stroke, 72 hemorrhagic stroke, and 20 of unknown origin). Neither ischemic nor hemorrhagic stroke risk was related to OC use, duration, or type of OC use, even among women who were smokers or hypertensive. Though not statistically significant, risk of hemorrhagic stroke was elevated in women who started using OCs after the age of 30 (Hazard Ratio [HR] 2.3, 95% CI 0.8 to 6.8) and women recommended by a doctor to stop using OC for medical reasons (2.1, 0.9 to 5.0) compared with never users. Compared with nulliparous women, parous women had a statistically significant lower risk of hemorrhagic stroke (0.5, 0.2 to 0.8), but similar association was not found for ischemic stroke (0.9, 0.5 to 1.4).

Conclusions—There was no significant association of OC use with ischemic or hemorrhagic stroke, and the parity was associated with reduced risk of hemorrhagic stroke but not with ischemic stroke.

Key Words: oral contraceptives ■ reproductive history ■ stroke ■ hemorrhagic ■ ischemic

Stroke is a public health problem throughout the world, including Sweden, where it is a leading cause of death and disability.1 Ischemic stroke accounts for 80% of all cases of stroke in Sweden, whereas intracerebral hemorrhagic stroke (10%) is more rare.1 The lower incidence among women than in men at all ages in Sweden1 implies a lower prevalence of established stroke risk factors.

The potential role for oral contraceptives (OC) and reproductive factors in the etiology of stroke has been extensively investigated, but not resolved. Concern about a link between OC use and stroke was first raised in the early 1960s around the time their use became common. Randomized controlled trials of OCs have not been conducted because of ethical constraints, but many case–control studies and some cohort studies have been undertaken to address this question. A recent meta-analysis by Chan et al showed no association (RR = 1.0, 95% CI 0.5 to 1.8) between OC use (combining current and former users) with stroke among 4 cohort studies, but found a statistically significantly increased risk (2.1, 1.6 to 2.9) among the 16 case–control studies2 which was confined mainly to ischemic (2.7, 2.2 to 3.4) rather than hemorrhagic stroke (1.3, 1.0 to 1.7). In that meta-analysis there was also evidence that risk estimates were more extreme among studies using hospital controls (2.9, 1.7 to 4.9) compared to studies using community controls (1.8, 1.4 to 2.3), which may be less prone to bias.2 Similar findings were also reported in the meta-analysis by Baillargeon et al, in which the increased risk of ischemic stroke among current OC users was higher for studies using hospital controls (2.4, 1.2 to 4.7) rather than population controls (1.7, 1.5 to 2.0).3 In contrast, an earlier meta-analysis by Gillum et al showed similarly increased risk of ischemic stroke across 3 cohort studies (3.2, 2.0 to 5.3; one of which was included in the Chan et al meta-analysis4) and 12 case–control studies (2.8, 2.2 to

Received July 17, 2008; final revision received October 10, 2008; accepted November 7, 2008.

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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.108.531913

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Materials and Methods

Study Participants and Data Collection

The Women’s Lifestyle and Health cohort provides a unique opportunity to investigate the impact of low dose OC use focusing on women in their older reproductive years, a group which has been rarely studied but who increasingly use OC and have an elevated baseline risk of stroke compared to younger women. Furthermore, we are able to distinguish between ischemic and hemorrhagic stroke, including more cases than in previous cohort studies on this topic. Our aim was to investigate the association between the reproductive history, OC use patterns and the risk of ischemic and hemorrhagic stroke among middle-aged Swedish women, using comprehensive assessment of risk factors and stroke outcome measures assessed through register data.

Exposure and Covariate Classification

Information collected on reproductive history included age at menarche, menstrual cycle length at age 30, age at first birth, and duration of breastfeeding. Information was also collected on OC use, including ever use, current use, total duration of use, and age at first use. Ever users were asked if they had used OC for reasons other than to prevent pregnancy and if they had ever been recommended to stop use for medical reasons. To facilitate recall, a color brochure with pictures of almost all OC packages ever sold in Sweden was sent to all women. Detailed information was also collected about each specific period of use, defined as any continuous use of one specific hormonal contraceptive brand. Up to 10 different periods of use were reported, with questions about age at starting, duration of use, and brand name.

We used questionnaire information to define the OC use status (never, former and current—defined as OC use within the previous year) and total duration of use. We also classified OC types according to the combined OC versus progestin-only pill. Among combined OC users, the estrogen dose (low-dose—ie, <50 μg ethinyl estradiol or <75 μg mestranol versus high dose) and the generation of progestin were further categorized. The following progestins were designated as “first generation”: norethisterone (norethindrone), norethynodrel, lynestrenol, and ethynodiol acetate. Norgestrel and levonorgestrel were designated as “second generation” progestins, and desogestrel was designated as “third generation.” Megestrol, quinestrol, chloradinone acetate, and cyproterone acetate were classified as “other progestins.”

Participants reported on established stroke risk factors at baseline, which were: Body Mass Index (BMI, <20, 20 to <25, 25 to <30, ≥30 kg/m²), years of education (<10, 10 to <13, 13 to <16, ≥16 years), alcohol consumption (none or by quintile of consumption: <1.25, 1.25 to 2.88, 2.88 to 5.49, ≥5.49 g/d), smoking status (current, former, never), pack years of cigarette smoking (never smoker, <5, 5 to <10, 10 to <15, 15 to <20, ≥20 pack years), physical activity (very low, low, normal, high, very high), high blood pressure (yes/no), and diabetes (yes/no). Women with missing data for previous stroke (n=3265), previous myocardial infarction (n=3277), diabetes (n=3101), or hypertension (n=2106) were assumed not to have prevalent disease at baseline.

Follow-Up and Stroke End Points

The followed-up for death and disease incidence among the study participants was mainly through linkages with existing nationwide health registers, using the individually unique national registration number of the women and the Swedish public and population-based health care system, so that follow-up was virtually complete with respect to death, emigration, and stroke. Information on stroke was collected through linkage to the National Hospital Discharge Register which used ICD-9 from 1987 to 1996 and the 10th version thereafter. We considered cases in the Inpatient Register with any of the following main diagnoses: ischemic stroke (occlusion of cerebral arteries, IS) (ICD7: 332; ICD8: 434 to 436; ICD9: 434; ICD10: I63.3 to I63.9), intracerebral hemorrhage (ICH, ICD7: 331; ICD8, 9: 431; ICD10: I61), and undefined stroke (ICD7: 334; ICD8, 9: 436; ICD10: I64). We also linked our cohort to the nationwide Causes of Death Register, as some patients might have suffered from sudden death attributable to stroke without previous hospitalization. We obtained information on date of death from other diseases from the Causes of Death Register and on date of emigration out of Sweden from the Emigration Register.

The start of follow-up was defined as the date of receipt of the returned questionnaire, and person-years were calculated until the first primary diagnosis of fatal or nonfatal stroke, date of emigration (n=690) or death, or the end of follow up (December 31, 2004), whichever came first. The average length of follow-up was 12.9 years. In total, there were 285 stroke events (193 ischemic, 72 hemorrhagic and 20 of unknown origin) and 764 women died from other causes.

Statistical Analysis

We assessed whether reproductive variables and OC use were associated with the age-adjusted incidence of ischemic and hemorrhagic stroke, in turn, by calculating hazard ratios (HRs) as estimates of relative risk, with associated 2-sided 95% confidence intervals (CI) with the Cox Proportional Hazards model. The attained age has been used as the time scale in the models.

The following reproductive history variables were considered, in turn: age at menarche (≤12, 13, ≥14 years), parity (nulliparous versus parous), and among parous women: age at first birth (<21, 21 to <25, ≥25 years), and duration of breastfeeding (<6, 6 to 12 or >12 months). The following OC use variables were considered, in turn, in the analysis: OC use status (never, current, former), total duration of OC use (<5, 5 to <10, 10 to <15, ≥15 years); age at first OC use (<20, 20 to <25, 25 to <30, ≥30 years), doctor ever recommended cessation of OC use for medical reasons; type of

3.5. Many trials have been undertaken to assess the effect of hormone replacement therapy (HRT) on stroke, and these findings could arguably be generalized to OC use. A meta-analysis of 28 trials showed a small but statistically significant increased risk of ischemic stroke among women taking HRT (1.3, 1.1 to 1.6) but no apparent increase in the risk of hemorrhagic stroke (1.1, 0.7 to 1.8).

There is a paucity of data on the role of other reproductive factors in the etiology of stroke. The few studies that have explored the relationship have generally failed to find an association between stroke and parity after multi-variable adjustment. One large case–control study showed an elevated risk of ischemic stroke among women with an early age at menarche or late age at menopause, which are factors that contribute to high lifetime estrogen exposure.

The Women’s Lifestyle and Health cohort provides a unique opportunity to investigate the impact of low dose OC use focusing on women in their older reproductive years, a group which has been rarely studied but who increasingly use OC and have an elevated baseline risk of stroke compared to younger women. Furthermore, we are able to distinguish between ischemic and hemorrhagic stroke, including more cases than in previous cohort studies on this topic. Our aim was to investigate the association between the reproductive history, OC use patterns and the risk of ischemic and hemorrhagic stroke among middle-aged Swedish women, using comprehensive assessment of risk factors and stroke outcome measures assessed through register data.
OC use (combined OC [COC] versus progestin-only pill [POP]); and among COC users: estrogen dose (low-dose versus high dose) and generation of progestin (second/third versus first generation).

The models were successively adjusted for established stroke risk factors, which were cigarette smoking, BMI, alcohol consumption, physical activity, diabetes, and hypertension. Subgroup analyses were conducted to assess whether the relationship between OC use and reproductive history was modified by the presence of stroke risk factors (ie, hypertension, diabetes, current smoking, or obesity). We tested for trends across categories of variables by assigning the median values to the categories and treating the exposures as continuous variables in the models. The proportional hazard assumption was checked by plotting the Schoenfeld residuals.15 Sensitivity analyses were undertaken to test whether the results were consistent in the subgroup of women for whom complete data were available for all variables examined. All tests of statistical hypothesis were made on the 2-sided 5% level of significance. The SAS software version 9.1 was used for all the statistical analyses.

**Ethics**

The study was approved by the Data Inspection Board in Sweden and by the regional Ethical Committee. Consent was assumed by the return of the postal questionnaire.

### Results

**OC Use and Reproductive History Characteristics**

At baseline, the mean age of the women was 40 years (SD=6). The majority of the cohort participants reported they had used OCs in the past (69%), whereas few were current OC users (15%) or had never used OCs (16%; Table 1). Women who had never used OCs tended to be older (mean age 42 years, SD: 6) than current (37.5) or former (40.5) users. Alcohol consumption was lower among women who had never used OCs, and they were also less likely to have ever smoked than former or current OC users, who had similar prevalence of these risk factors. The summary statistics indicate that stroke risk factors (BMI, education, physical activity, hypertension or diabetes) and reproductive variables (age at menarche, menstrual cycle, age at first birth, or months of breastfeeding) were similarly distributed among current, former, and never users of OCs, except that nulliparity was more common among women who had never used OCs.

The estimated mean duration of OC use was approximately twice as long in current users of OC (11 years±6) compared...
to former users (6 years ± 5; Table 2). The majority of women started using OCs in their teenage years. Approximately 1 in 4 current OC users and 1 in 5 former OC users had used OC for a reason other than to prevent pregnancy, although the specific reason was not available. Few current (7%) or former (15%) OC users had ever been told by a doctor to stop using OCs for medical reasons. Most current and former OC users relied exclusively on combined OCs (70% and 65%, respectively). Fewer former OC users relied solely on progestin-only pills (2%), whereas this was relatively common among current users (24%). Among OC users, current OC users were likely to take second or third generation of progestin (84%) with only low doses of estrogen (88%), whereas fewer former users of COCs used second or third generation of progestin only (47%) or low doses of estrogen exclusively (21%).

### Fatal and Nonfatal Total Stroke

When ischemic and hemorrhagic stroke were combined together with stroke of unknown origin, risk of fatal and nonfatal total stroke was significantly higher among women with menarche below age 13 (1.5, 1.1 to 2.1). There was also a significant lower risk of stroke among parous women compared to nulliparous women (0.7, 0.5 to 1.0), or women who had breastfed for at least a year, compared to less than 6 months (0.7, 0.4 to 1.0). The remaining reproductive and OC variables were not related to risk of stroke, when all types of stroke were combined (data not shown). Comparison of the time-to-event Kaplan–Meier survival curves showed no difference for never OC users, former OC users, and current OC users for developing fatal or nonfatal stroke.

### Ischemic Stroke

The occurrence of ischemic stroke was not statistically significant related to age at menarche or parity (Table 3). There was a statistically significantly inverse association of ischemic stroke incidence with older age at first birth (age ≥ 25 versus age 21 to 24 years: HR = 0.6, 0.4 to 0.9) as well as with duration of breastfeeding (>12 months versus <6 months: 0.5, 0.3 to 0.8); both of these associations disappeared after multivariable adjustment (0.7, 0.4 to 1.1 and 0.7, 0.4 to 1.2, respectively). Former and current OC users were not at statistically significantly higher risk of ischemic stroke compared to never users (0.9, 0.6 to 1.4 and 1.1, 0.6 to 2.0 respectively). The other OC variables were also not statistically significantly associated with ischemic stroke, including duration of OC use, age at first use, type of OC use (including progestin generation and estrogen dose; data not shown) or doctor recommendation to stop using OC for medical reasons.

### Hemorrhagic Stroke

Age at menarche was also unrelated to the occurrence of hemorrhagic stroke (Table 4). Parous women had a significantly lower risk than nulliparous women, even after multivariable adjustment (0.5, 0.2 to 0.9). Women who gave first birth at age ≤ 21 had twice the risk of hemorrhagic stroke compared with those who gave first birth later (2.0, 1.0 to 4.0), although this was no longer statistically significant after multivariable adjustment (1.8, 0.8 to 4.1). Similar to the association with ischemic stroke, women who breastfed more than 1 year had a lower risk of hemorrhagic stroke than women who breastfed less than 6 months, though this was not statistically significant (0.6, 0.3 to 1.3). There was no clear association between OC use status nor duration of OC use with incidence of hemorrhagic stroke. Women who started using OCs after the age of 30 were at increased risk of hemorrhagic stroke (2.7, 1.0 to 7.5) as were women who had been told by a doctor to stop using OCs (2.6, 1.2 to 5.7) compared to never users, although these associations were no longer statistically significant after adjustment for covariates. There was no apparent association between the type of OC used (including progestin generation and estrogen dose; data not shown) and the occurrence of hemorrhagic stroke.

### Stratification by Stroke Risk Factors

The association between reproductive factors, OC use, and risk of stroke was stratified by the presence of other stroke risk factors, which included current smoking, hypertension, diabetes, or obesity (BMI > 30 kg/m²), to assess whether risks were elevated by the presence of other stroke risk factors (Table 5). We found essentially no difference in the risk of either ischemic or hemorrhagic stroke associated with reproductive factors or OC use, including age at first birth, breastfeeding duration, duration of OC use, type of OC use, or doctor recommended stopping taking OC (data not shown). The impact could not be assessed on estrogen dose and
progestin generation as the numbers were too small to allow meaningful analyses (data not shown). Furthermore, there was no difference between smokers and nonsmokers in the association between current or former OC use compared to never users and risk of ischemic and hemorrhagic stroke (data not shown).

### Sensitivity Analyses
The sensitivity analyses restricting the analyses to women with complete data for all variables of interest \( (n=37,068, \text{total number of strokes}=217) \) showed no difference in results compared to the analyses from the full dataset (data not shown).

### Table 3. Relative Risk of Fatal or Nonfatal Ischemic Stroke, According to Different Reproductive Factor and Patterns of Oral Contraceptive Use

<table>
<thead>
<tr>
<th>Reproductive history</th>
<th>No. of Subjects</th>
<th>Stroke Cases</th>
<th>Age-Adjusted RR</th>
<th>Multivariable Adjusted RR*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Menarche age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤12</td>
<td>16,927</td>
<td>76</td>
<td>1.3 (0.9–1.9)</td>
<td>1.4 (0.9–2.2)</td>
</tr>
<tr>
<td>Age 13</td>
<td>13,586</td>
<td>49</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Age ≥14</td>
<td>14,653</td>
<td>66</td>
<td>1.1 (0.8–1.6)</td>
<td>1.1 (0.7–1.7)</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td></td>
<td></td>
<td>0.29</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>6,435</td>
<td>28</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Parous</td>
<td>39,294</td>
<td>165</td>
<td>0.8 (0.5–1.2)</td>
<td>0.9 (0.5–1.4)</td>
</tr>
<tr>
<td><strong>Parous women only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;21</td>
<td>11,942</td>
<td>68</td>
<td>1.1 (0.7–1.5)</td>
<td>1.0 (0.6–1.5)</td>
</tr>
<tr>
<td>Age 21–25</td>
<td>9,905</td>
<td>49</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Age ≥25</td>
<td>17,444</td>
<td>48</td>
<td>0.6 (0.4–0.9)</td>
<td>0.7 (0.4–1.1)</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Breast feeding duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>10,823</td>
<td>64</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>6–12 months</td>
<td>14,797</td>
<td>69</td>
<td>0.9 (0.6–1.2)</td>
<td>1.1 (0.7–1.6)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>13,671</td>
<td>32</td>
<td>0.5 (0.3–0.8)</td>
<td>0.7 (0.4–1.2)</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Oral contraceptive use#</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OC use status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never OC user</td>
<td>7,471</td>
<td>44</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Current OC user</td>
<td>6,794</td>
<td>20</td>
<td>0.9 (0.5–1.6)</td>
<td>1.1 (0.6–2.0)</td>
</tr>
<tr>
<td>Former OC user</td>
<td>31,464</td>
<td>129</td>
<td>0.9 (0.6–1.2)</td>
<td>0.9 (0.6–1.4)</td>
</tr>
<tr>
<td><strong>Current/Former OC users only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of OC use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used &lt;5 years</td>
<td>16,262</td>
<td>74</td>
<td>0.9 (0.6–1.3)</td>
<td>1.0 (0.6–1.5)</td>
</tr>
<tr>
<td>Used 5–9 years</td>
<td>10,568</td>
<td>24</td>
<td>0.5 (0.3–0.9)</td>
<td>0.6 (0.4–1.2)</td>
</tr>
<tr>
<td>Used ≥10 years</td>
<td>10,877</td>
<td>45</td>
<td>1.0 (0.6–1.4)</td>
<td>1.2 (0.7–1.9)</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td></td>
<td></td>
<td>0.43</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>Age of first use OC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;20</td>
<td>22,065</td>
<td>62</td>
<td>0.9 (0.6–1.3)</td>
<td>0.9 (0.6–1.5)</td>
</tr>
<tr>
<td>Age 20–24</td>
<td>11,228</td>
<td>59</td>
<td>0.9 (0.6–1.3)</td>
<td>1.0 (0.6–1.6)</td>
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<tr>
<td>Age 25–30</td>
<td>3,212</td>
<td>17</td>
<td>0.8 (0.4–1.3)</td>
<td>1.0 (0.5–1.8)</td>
</tr>
<tr>
<td>Age &gt;30</td>
<td>1,445</td>
<td>7</td>
<td>0.7 (0.3–1.6)</td>
<td>1.1 (0.5–2.4)</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td></td>
<td></td>
<td>0.25</td>
<td>0.97</td>
</tr>
<tr>
<td>Doctor ever recommend stop using OC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>32,329</td>
<td>109</td>
<td>0.8 (0.5–1.1)</td>
<td>0.9 (0.6–1.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>5,284</td>
<td>39</td>
<td>1.4 (0.9–2.2)</td>
<td>1.2 (0.7–2.0)</td>
</tr>
</tbody>
</table>

*Adjusted for BMI, education, alcohol drinking, smoking status, pack-years of smoking, physical activity, high blood pressure, and diabetes.

#Never OC user group was used as the reference for all OC related analysis.
Discussion

In this large prospective study of middle-aged Swedish women, neither OC use nor reproductive factors was found to be associated significantly with risk of ischemic stroke. With respect to hemorrhagic stroke, overall there was not significant association with OC use, duration or type of OC use, but the risk was significantly elevated among women who started using OCs late, who stopped using OCs for medical reasons, and who were nulliparous. These associations were partially explained by established stroke risk factors, and so may have occurred through confounding. Furthermore, given the small number of cases involved and large number of subgroup
analyses conducted, much of the association observed for hemorrhagic stroke could well be due to play of the chance.

Our findings are broadly consistent with the published meta-analysis of cohort studies, which showed no association between OC use and stroke risk in 4 cohort studies.2 Previous analyses of the same data from the Women's Lifestyle and Health cohort showed no association between former or current OC use and risk of MI,16 and because there are similarities between the etiology of MI17 and ischemic stroke,18 this also is consistent with the current findings.

There is some biological rationale for the purported association between current OC use and stroke risk. It is known that OCs can exert thrombotic or inflammatory effects,19 which could increase the risk of ischemic stroke, though not hemorrhagic stroke. The earlier OC preparations contained higher doses of ethinyl estradiol (80 to 100 μg) than preparations now popular (20 to 35 μg estrogen), so that earlier formulations in particular were expected to be more closely linked to stroke risk. The cohort studies included in the Chan et al review,2 which showed no impact on stroke risk, were conducted more recently and included women taking a lower dose of estrogen compared with women included in the Gillum review,5 which showed a statistically significant relationship with stroke risk. However, in combined analyses of cohort and case–control studies, the meta-analysis by Chan et al2 did not show a stronger effect of high dose estrogen OC on stroke (1.8, 1.4 to 2.3) compared to low dose (1.8, 1.4 to 2.3), whereas in the Gillum et al review5 the risk was twice as high for women taking high doses of estrogen (4.5, 2.2 to 9.5) rather than low dose (2.1, 1.6 to 2.8). Similarly, the review by Baillargeon et al showed a higher increased risk of ischemic stroke among second generation compared to third generation OC users.3 Our findings support those of Chan et al, as there was no relationship overall between OCs and stroke, and no impact of estrogen dose. Most of the current OC users in our cohort were taking low-dose estrogen and second- or third-generation progestins, but previous studies have not suggested that the type of progestin has an impact on stroke risk. In combined analyses of cohort and case–control studies, the 2 meta-analyses both showed a stronger association between OC use and stroke for women with established stroke risk factors, defined as smokers or those with high blood pressure, which was not supported by our findings.2,5

Few studies have assessed the relationship between reproductive history and stroke. Results from a large case–control study showed an elevated risk of ischemic stroke among women with an early age at menarche or late age at menopause, contributing to high lifetime estrogen exposure.12 A cohort study from Finland showed a 4-fold higher mortality from hemorrhagic stroke among women with ≥10 births compared to women with 2 to 4 births.9 The first National Health and Nutrition Examination Survey Epidemiology Follow-up Study also showed a higher risk of stroke among women who had ≥6 pregnancies, although this association attenuated after adjustment for stroke risk factors (1.3, 0.9 to 1.9).10 A British case–control study also failed to show an association between parity and risk of stroke.11

Our study has several limitations. OC use and reproductive history were only measured at baseline. Parity may therefore have changed subsequently during follow-up.
relationship between reproductive history and ischemic stroke. The significant associations observed between certain measures of OC or of reproductive history with hemorrhagic stroke is unexplained and have little biological plausibility, and may well be attributable to play of chance, especially given the very small number of cases involved.

Acknowledgments
We thank all the women who contributed to this study.

Sources of Funding
The survey was supported by the Swedish Council for Planning and Coordination of Research, Swedish Cancer Society, STINT (The Swedish Foundation for International Cooperation in Research and Higher Education) Organon, Pharmacia, Medical Products Agency and Schering-Plough. The authors’ work was independent of the funders.

Disclosures
None.

References

Summary
Use of OC is increasing among women in their later reproductive years, and its potential impact on health is of great public health significance. In this large prospective study of middle-aged women, we did not find any apparent association between ischemic stroke or hemorrhagic stroke risk with OC use. We also failed to find any significant

However, this is only likely to have affected the women aged <35 years, who made up 22% of the cohort, and only 22% of whom were nulliparous at baseline. Similarly, OC use at baseline may not have been reflective of OC use during follow-up so that nondifferential misclassification could occur which would underestimate any potential association between current OC use and risk of stroke. In contrast, the two main cohort studies cited by Chan et al updated OC information during follow-up. Confounding may have played a role in this study because ever users of OC had higher alcohol intake and were more likely to be smokers than never users, although there was no elevated risk of stroke even in the age-adjusted analyses. In addition, there may have been residual confounding as covariates were only measured at baseline and some potentially important stroke risk factors were not measured in the study, such as childhood socioeconomic conditions, cholesterol and fibrinogen levels, migraine with aura, atrial fibrillation, drug use, and cerebrovascular disorders. Our self-administered questionnaire was not systematically validated, although previous studies have suggested that self-report of OC use by women is reasonably accurate, particularly when supplemented by visual memory aids. We did not include women who were postmenopausal at baseline and no information was available for remaining premenopausal women about their menstrual status during the follow-up, so that we were unable to assess the effect of menopausal status on stroke risk, nor the effect of lifetime estrogen exposure. However, a study of 19731 postmenopausal Norwegian women found that ischemic and hemorrhagic stroke were unrelated to age at natural menopause.21

There were also strengths of our study. We simultaneously assessed the role of both OC use and reproductive factors in relation to stroke. Stroke is a heterogeneous condition, and the association with OC use and reproductive history may differ importantly between different types of stroke. We used registry data to measure incident stroke among women who were disease-free at baseline, resulting in virtually complete assessment of outcomes, and we measured OC use and reproductive history before the stroke events occurred. Because of its large size and prolonged follow-up, the number of stroke cases involved in the study was larger compared with earlier cohort studies. Previous analyses from this cohort confirmed the increased risk of ischemic stroke among women who smoked, and those with lower educational levels, indicating that there was sufficient power to identify real effects. Moreover, the women in the cohort were likely to be representative of the general population in terms of risk factor profiles, making the results more generalizable.

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Stroke, published online February 10, 2009;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2009/02/10/STROKEAHA.108.531913.citation

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